

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 7/16, 7/48, 7/06, 7/00, A23L 1/226, A23G 3/30	A1	(11) International Publication Number: WO 95/07683 (43) International Publication Date: 23 March 1995 (23.03.95)
(21) International Application Number: PCT/US94/10044 (22) International Filing Date: 7 September 1994 (07.09.94) (30) Priority Data: 08/123,484 17 September 1993 (17.09.93) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors: EIS, Michael, Johannes; 3841 Trevor Avenue, Cheviot, OH 45211 (US). NELSON, Dennis, George, Anthony; 8485 Rupp Farm Drive, West Chester, OH 45069 (US). THOMPSON, James, Edwin; 11790 Tennyson Drive, Sharonville, OH 45241 (US). HAYES, Jeffrey, Charles; 83 Bishops Gate Drive #206, Cincinnati, OH 45246 (US). STUART, Dorothy, Jean; 1775 Leway Drive, Fairfield, OH 45014 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).		(81) Designated States: AU, BR, CA, CN, JP, PL, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: COMPOSITION CONTAINING PHOSPHATE DERIVATIVES (57) Abstract The subject invention encompasses compositions in a form suitable for oral or topical administration comprising one or more phosphate derivatives, carrier materials and preferably a safe and effective amount of one or more actives.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

COMPOSITION CONTAINING PHOSPHATE DERIVATIVES

5

BACKGROUND OF THE INVENTION

The present invention relates to compositions comprising one or more phosphate derivatives, and carrier materials wherein the compositions are in a form suitable for oral or topical administration. These compositions preferably contain a safe and effective amount of one or more active materials such as those which provide nutritional, therapeutic, antimicrobial, pharmaceutical, medicinal, and/or aesthetic benefit, and those commonly used in health care products.

A wide variety of flavor, coolant and sweetener agents are used in consumer and health care products today. Aesthetic qualities of these compositions such as taste, smell, mouthfeel, and after-taste are important concerns for consumer acceptability. Products with poor flavor, a bad after-taste or other negative aesthetics may limit consumer acceptability initially or over an extended period of time, thereby limiting consumer usage and compliance with treatment regimens.

An additional aspect of consumer acceptability and compliance is the consumer's perception of efficacy. Consumer satisfaction with a product is likely to be increased if some type of sensory signal exists to remind the consumer that the product is working after ingestion, administration or expectoration.

It has been discovered that phosphate derivatives comprising flavor, coolant, and/or sweetener components may be incorporated into oral or topical compositions to deliver pleasing aesthetics and high consumer acceptability. It has also been discovered that these compositions for oral or topical administration may be formulated to include a safe and effective amount of one or more actives. These compositions may provide sustained coolant, flavor and/or sweetener activity, depending on the particular derivative being used. These phosphate derivatives may also serve to improve the aesthetics of the compositions and provide a sensory signal to the user.

It is therefore an object of the present invention to provide compositions that are aesthetically pleasing to the consumer. It is also an object of the present invention to provide compositions which provide a sensory signal to the user, and preferably contain a safe and effective amount of one or more actives.

These and other objects of the present invention will become readily apparent from the detailed description which follows.

All percentages and ratios used herein are by weight, and all measurements are made at 25C, unless otherwise specified.

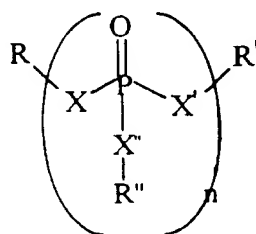
5

SUMMARY OF THE INVENTION

The present invention relates to compositions comprising:

(a) from about 0.001% to about 25% of one or more phosphate derivatives having the formula:

10



wherein R is selected from the group consisting of a coolant component, a sweetener component, and a flavorant component;

15

wherein R' and R'' are independently selected from the group consisting of R, an adherent component, M⁺, M⁺⁺, C⁺, and hydrogen;

wherein X, X', and X'' are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

wherein n is an integer from 1 to 3; and

20

(b) from about 75% to about 99.999% of carrier materials; and wherein further the compositions are in a form suitable for oral or topical administration.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention relates to a composition comprising one or more phosphate derivatives, and carrier materials wherein the compositions are in a form suitable for oral or topical administration. These compositions also preferably contain a safe and effective amount of one or more actives.

25

30

The term "active" as used herein means an agent which provides an effect greater than an excipient such as agents providing nutritional, therapeutic, antimicrobial, pharmaceutical, medicinal, and/or aesthetic benefit and those commonly used in health care products.

The phrase "suitable for oral or topical administration" as used herein means any formulation that is suitable for the convenient administration of the composition whereby the composition is intentionally swallowed, chewed, ingested, retained in the

oral cavity for any period of time, placed in contact with internal mucous membranes of the body, such as those of the nose, mouth, or throat whether by direct or indirect application or inhalation to the nasal passages, or applied to the surfaces of the skin for therapeutic reasons or reasons other than for cosmetic benefit.

5 The phrase "a safe and effective amount", as used herein, means a sufficient amount of material to provide the desired benefit without undue adverse side effects (such as toxicity, irritation or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific safe and effective amount will vary with such factors as the particular condition that is being
10 treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), and the specific formulation and optional components employed.

The components for use in the present compositions and the preferred amounts to be utilized are described in detail hereinafter.

15 **Phosphate Derivatives:**

The present invention compositions contain one or more phosphate derivatives. These compounds may be formulated by phosphorylating a least one coolant, sweetener or flavorant component. These compounds also include linking at least one coolant, sweetener or flavorant component to an adherent component via a
20 phosphate bridge. In addition, pyrophosphate and triphosphate groupings may be substituted for the phosphate group. Coolant, flavorant, or adherent components may also be linked to phosphorous via two functional groups or attachment sites. Furthermore, the phosphate derivatives described above may be bound via Coulombic interaction with charged compounds or materials, including polymers.

25 The present compositions may deliver the desired coolant, flavorant and/or sweetener qualities through the action of the phosphate derivative itself. The compositions may also provide a sustained effect through the release of the coolant, flavorant and/or sweetener component from the molecule after cleavage of the phosphate from the coolant flavorant and/or sweetener by phosphatase enzymes.
30 The phosphatase enzymes include but are not limited to acid, basic, and pyrophosphatases.

The term "coolant component" as used herein refers to coolant compounds having a hydroxy, amino, or thiol functionality which is capable of forming an ester, amido, or thioester linkage with a phosphorus(V) atom. Preferred coolant
35 components are selected from the group consisting of menthol, 3-l-menthoxypropane-1,2-diol ("TK-10"), menthone glycerol acetal ("MGA"), and

menthyl lactate. The terms "menthol" and "menthyl" as used herein include dextro- and levorotatory isomers of these compounds and racemic mixtures thereof.

The term "flavorant component" as used herein refers to flavorant compounds having a hydroxy, amino, or thiol functionality which is capable of forming either an ester, amido, or thioester linkage with a phosphorus(V) atom. Preferred flavorant compounds are selected from the group consisting of methyl salicylate, eugenol, vanillin, thymol, cinnamaldehyde glycerol acetal ("CGA"), and linalool.

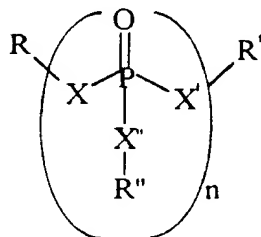
The term "sweetener component" as used herein refers to sweetener compounds having a hydroxy, amino, or thiol functionality which is capable of forming either an ester, amido, or thioester linkage with a phosphorus(V) atom. Preferred sweetener components are saccharin, mannitol, sorbitol, glucose, sucrose, fructose, and neohesperidin dihydrochalcone.

The term "adherent component" as used herein refers to either monomers, oligomers, or polymers having hydroxy, amino, or thiol functionalities which are capable of forming either ester amido, or thioester linkages with phosphorus(V) atoms. The monomers, oligomers, or polymers may also possess additional hydroxy, amino, or thiol groups which may either remain unsubstituted or be linked via ester amido, or thioester linkages to a phosphorus(V) atom which is also attached to a coolant, flavor, or active portion. Preferred compounds are selected from the group consisting of C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate/ethylene copolymer, cellulose, chitin, glucose, glucosamine, silica gel, glycerol, and lower alkyl vinyl ether-maleic acids.

The terms "M+" and "M++" as used herein refer to physiologically relevant metal cations. The phrase "physiologically relevant metal cations" as used herein refers to metal cations that are significant to the organic or bodily processes of a human or lower animal. Preferred "M+" cations are sodium and potassium. Preferred "M++" cations are calcium, zinc, magnesium, manganese, copper, and stannous.

The term "C+" as used herein refers to an "organic" cation. An "organic" cation as used herein refers to cations that contain positively charged nitrogen, phosphorus, oxygen, or sulfur atoms. Such cations may contain more than one positively-charged site and in the case of oligomers or polymers containing nitrogen, phosphorus, oxygen, or sulfur atoms, many positively-charged centers may exist. Preferred "organic" cations include ammonium, protonated amines such as protonated glucosamine, and partially or fully protonated amine-containing polymers such as protonated chitosan.

The phosphate derivatives of this invention are represented by the following formula:



5

In the above formula,

R is selected from the group consisting of a coolant component, a sweetener component, and a flavorant component;

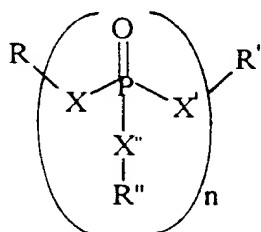
R' and R'' are independently selected from the group consisting of R, an adherent component, M⁺, M⁺⁺, C⁺, and hydrogen;

X, X', and X'' are independently selected from the group consisting of oxygen, nitrogen, and sulfur; and

n is an integer from 1 to 3.

In addition, R' may equal R'', preferably wherein R' and R'' are selected from the group consisting of calcium, zinc, and magnesium, manganese, copper and stannous.

Preferred phosphate derivatives have the formula:



20

In the above formula:

R is selected from the group consisting of menthol, TK-10, MGA, menthyl lactate, methyl salicylate, saccharin, mannitol, sorbitol, glucose, sucrose, fructose, neohesperidin dihydrochalcone, eugenol, vanillin, thymol, CGA, and linalool;

R' and R'' are independently selected from the group consisting of R, C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate-ethylene co-polymer, cellulose, chitin, glucosamine, silica gel, glycerol, lower alkyl vinyl ether-maleic acids, sodium, potassium, calcium, zinc, magnesium, manganese, copper and stannous, ammonium,

protonated amines, partially or fully protonated amine-containing polymers, and hydrogen;

X, X', and X" are independently selected from the group consisting of oxygen, nitrogen, and sulfur; and

5 n is an integer from 1 to 3.

In addition, R' may equal R", preferably wherein R' and R" are independently selected from the group consisting of calcium, zinc, magnesium, manganese, copper and stannous.

10 Most preferred phosphate derivatives are menthyl monophosphate, eugenyl monophosphate, thymyl monophosphate, l-menthyl diphosphate, bis l-menthyl pyrophosphate, and l-menthyl triphosphate. The phosphate derivatives are used in the present invention at levels of from about 0.001% to about 25%, preferably from about 0.01% to about 15%, by weight of the composition.

Carrier Materials:

15 In formulating the compositions of this invention the phosphate derivative will be incorporated into a carrier which may be completely inert or which may contain other active ingredients. The term "carrier materials", as used herein, means one or more compatible substances suitable for administration to a human or lower animal. The term "compatible", as used herein means that the components of the
20 compositions are capable of being commingled with phosphate derivatives, actives, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the present compositions under ordinary use situations. Carrier materials must also be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal
25 being treated.

A wide variety of carriers will be suitable depending upon the end use of the compositions. The phosphate derivatives can be incorporated into a range of compositions generally divided into oral and topical compositions, both terms being meant in their broadest possible sense. Oral compositions include not only foodstuffs
30 and beverages taken into the mouth and swallowed, but also other orally ingested compositions taken into the mouth for reasons other than for sustenance. Such compositions include (but are not limited to) solid oral dosage forms such as tablets, tablet coatings, caplets, hydrogels, and liquid oral dosage forms such as syrups, emulsions and suspensions. Oral compositions also include those compositions
35 which are taken into the mouth but are not necessarily swallowed, e.g. chewing gum.

Topical compositions include compositions applied to, or which in normal usage come in contact with, the internal membranes of the body such as those of the

nose, mouth, or throat, whether by direct or indirect application. Such compositions include (but are not limited to) nasal sprays, dentifrices, oral rinses, lozenges, foams, gels, and throat sprays. Topical compositions may also be compositions applied to the external surfaces of the body for therapeutic reasons or reasons other than for cosmetic benefit. Such compositions include ointments, lotions, gels, and creams. Preferred compositions of the present invention are health care compositions such as dentifrices, oral rinses, liquid oral dosage forms and nasal sprays.

The present compositions preferably comprise from about 75% to about 99.999%, and preferably from about 85% to about 99.99%, by weight of the composition. Suitable carrier materials herein, depending on intended end use, are selected from the group consisting of solvents, suspending agents, solubilizing agents, diluents, surfactants, buffers, lubricants, thickeners, emulsifiers, flavoring agents, colorants, humectants, sweeteners, co-solvents, binders, disintegrating agents, flow-inducing agents, coolants, plasticizers, wetting agents, antioxidants, stabilizers, and tableting agents.

Dentifrices

Dentifrice compositions may be of the liquid, paste, powder or gel type. These compositions will usually comprise a finely divided abrasive or polishing material, e.g. precipitated chalk, silica, magnesium silicate, calcium polymetaphosphate, aluminum hydroxide or other similar materials well known in the art. Abrasive materials are more fully described in U.S. Patent 3,070,510, Cooley et al., December 25, 1962, which is incorporated herein by reference. Toothpaste compositions additionally contain a surfactant or foaming agent. Suitable surfactants are those which are reasonably stable and foam throughout a wide pH range, including non-soap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. These surfactants are disclosed by Gieske et al. in U.S. Patent 4,051,234, issued September 27, 1977, also incorporated herein by reference.

Water is also present in the dentifrice compositions. Water employed should preferably be deionized and free from organic impurities. Water generally comprises from about 10% to about 50%, and preferably from about 20% to about 40%, by weight of the compositions. These amounts of water include the free water which is added plus that which is introduced with other materials such as with sorbitol.

Optional ingredients in dentifrice compositions include flavoring agents, colorants, buffers, lubricants, thickeners, emulsifiers or plasticizers, and humectants. Dentifrice carrier materials typically comprise from about 50% to about 94%, and preferably from about 60% to about 80%, by weight of the dentifrice compositions.

Oral Rinses

Oral rinses usually comprise an aqueous, alcoholic, or aqueous-alcoholic solution of an antiseptic which is often colored or flavored for palatability. Optional ingredients include humectants, surfactants, sweeteners, emulsifying agents, fluoride ion sources, tartar control, and anti-plaque agents. Oral rinse products may also be formed by dissolving a powder or tablet containing stannous gluconate in water just prior to use.

Oral rinse compositions typically are based on a water/ethanol solution having a ratio of water:ethanol of from about 20:1 to about 2:1. Humectants, such as glycerin and sorbitol, are usually included to give a moist feel to the mouth. Conventional oral rinse compositions generally comprise, by weight of the composition, from about 0% to 60% ethyl alcohol, 0% to 20% of a humectant, 0% to 2% emulsifying agents, 0% to 0.5% sweetening agents, 0% to 0.3% flavoring agents and the balance water.

Liquid Oral Dosage Forms

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, pseudo emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules. These dosage forms also contain suitable solvents, emulsifying agents, buffering agents, suspending agents, diluents, natural and artificial sweeteners, coloring agents, and flavoring agents. Antioxidants such as butylated hydroxy anisole or butylated hydroxy toluene, and preservatives such as methyl or propyl paraben or sodium benzoate may also be included. Specific examples of carriers and excipients that may be used to formulate oral dosage forms, are described by Roberts in U.S. Patent 3,903,297, issued September 2, 1975, which is incorporated herein by reference.

Since many of the actives are generally used in the form of a water-soluble salt, they can be readily incorporated into conventional aqueous-based formulations. Water-insoluble or poorly soluble actives, generally in base form, may also be incorporated into aqueous-based orally acceptable carriers such as dispersions, suspensions, oil-in-water emulsions and the like by means of suitable dispersing, suspending or emulsifying agents, respectively, which are readily apparent to those skilled in the art of formulations.

In preparing the liquid oral dosage forms, the active components are incorporated into an aqueous-based orally acceptable carrier consistent with conventional practices. An "aqueous-based orally acceptable carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is a suspension or solution

of the phosphate derivative and active in an aqueous vehicle containing a suitable suspending or solubilizing agent. Suitable suspending agents include celluloses, carboxymethyl cellulose and its salts, guar gum and the like. Suitable solubilizing agents include sucrose solutions, ethanol, and surfactants such as polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides (e.g., Polysorbate 80). Suspension systems, suspension and solubilizing agents, and methods for their use are described in M. Pernarowski, "Solutions, Emulsions and Suspensions" Remington's Pharmaceutical Sciences (A. Osol, editor, 15th Edition, 1975), which is incorporated herein by reference. While the amount of water in the compositions of this invention can vary over quite a wide range depending upon the total weight and volume of the essential ingredients and other optional ingredients, the total water content will generally range from about 20% to about 75%, and preferably from about 20% to about 40%, by weight of the composition.

Although water itself may make up the entire carrier, typical oral formulations also contain a co-solvent including but not limited to alcohol, propylene glycol, glycerin, sorbitol solution, and the like, to assist solubilization and incorporation of water-insoluble ingredients, flavoring oils and the like into the composition. In general, the compositions preferably contain from about 5 to about 25 volume/volume percent of the co-solvent, most preferably from about 10 to about 20 volume/volume percent of the co-solvent.

Nasal Sprays

Carriers suitable for nasal administration provide a product which is delivered to the nasal passages. Such carriers may be for example, aqueous or aerosol and are more fully described in Remington's Pharmaceutical Sciences (17th Edition, 1985), which is incorporated herein by reference. Such product forms include (but are not limited to) nasal solutions for use as drops or as sprays, nasal suspensions, nasal ointments, nasal gels, or other vehicles suitable for nasal administration.

Preferred nasal dosage forms are solutions, suspensions, and gels, which normally contain sodium chloride in a major amount of water (preferably purified water). Other ingredients including but not limited to: pH adjusters such as sodium hydroxide; emulsifiers or dispersing agents; buffering agents such as sodium bicarbonate; preservatives such as benzyl alcohol, parabens, benzalkonium chloride, chlorhexidine gluconate and disodium EDTA; agents for regulating isotonicity such as sodium chloride, boric acid, potassium phosphate and propylene glycol; wetting agents; thickening agents such as methylcellulose, xanthan gum, carboxymethyl cellulose, and carbomer; humectants such as sorbitol, propylene glycol, sorbitol, and

glycerol; surfactants such as polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides; and mixtures thereof, may also be present.

Solid Oral Dosage Forms

The present composition may also be in a solid oral dosage form. Tablets can
5 be compressed, triturated, freeze dried, sugar-coated, film-coated or multiple compressed. The tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents. In general, carrier materials suitable for the preparation of unit
10 dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms", Modern
15 Pharmaceutics, volume 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated herein by reference. Techniques and compositions for making tablets, capsules, and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference.

Lozenges and Chewing Gums

Other embodiments of the subject invention include lozenges and chewing
20 gums. Lozenge compositions comprise a lozenge carrier (i.e. a candy base). Candy bases are disclosed in U. S. Patent 4,472,373, Ryan, issued September 18, 1984, and in U.S. Patent 4,083,955, Grabenstetter et al., issued April 11, 1978. Chewing gum compositions comprise a chewing gum carrier such as those which are disclosed in these same patents, both of which are incorporated herein by reference. Chewing
25 gum carriers may comprise, for example, a gum base, flavoring agents, and sweetening agents.

Other Carriers

The invention compositions may be formulated with a wide variety of carrier materials in addition to those already disclosed. Some examples of substances which
30 can serve as carrier materials are sugars such as lactose, glucose, and sucrose; starches such as cornstarch and potato starch; cellulose and its derivatives such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; stearic acid; magnesium stearate; dicalcium phosphate; calcium sulfate; mineral oil and vegetable oils such as peanut oil, cottonseed oil,
35 sesame oil, olive oil, corn oil, and oil of theobroma; silicones such as siloxanes, silicon oils, fluids, gums and greases, and 1 or 2 part Room Temperature Vulcanizable; polyols such as propylene glycol, glycerin, sorbitol, mannitol,

polyethylene oxide, and polyethylene glycol; agar; karaya gum; alginic acid; as well as other non-toxic compatible substances used in consumer or health care formulations.

5 Coolant materials may also be included as carrier materials in the invention compositions. Preferred coolants in the present compositions are the paramenthane carboxamide agents such as N-ethyl-p-menthane-3-carboxamide, (known commercially as "WS-3"), and 3-l-menthoxypropane-1,2-diol (known commercially as "TK-10"), and mixtures thereof. These coolants are described in PCT Patent Application Publication WO 92-17164, to Upson et al., published October 15, 1992.
10 TK-10 is also described in U.S. Patent 4,459,425 to Amano et al., issued July 10, 1984; and WS-3 and other parmenthane carboxamides agents are described in U.S. Patent 4,136,163 to Watson et al., issued January 23, 1979. The disclosures of all three of these patent publications are incorporated by reference herein in their entirety.

15 When desired or necessary, suitable binders, lubricants, and disintegrating agents can also be incorporated in the compositions. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia sodium alginate, carboxymethylcellulose, microcrystalline cellulose, polyethylene glycol and waxes. Lubricants may include, for example, starch, methylcellulose,
20 agar, bentonite, guar gum, etc. Wetting agents such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, sweetening agents, excipients, tableting agents, stabilizers, antioxidants, and preservatives can also be present.

Active:

25 The invention compositions may also contain a safe and effective amount of one or more actives. Some actives that are useful in these compositions include (but are not limited to) antimicrobial agents such as iodine, sulfonamides, mercurials, bisbiguanides, or phenolics; antibiotics such as tetracycline, neomycin, kanamycin, metronidazole, or clindamycin; anti-inflammatory agents such as aspirin, acetaminophen, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or
30 hydrocortisone; immune-suppressive or stimulatory agents such as methotrexate or levamasole; dentinal desensitizing agents such as potassium nitrate, strontium chloride or sodium fluoride; odor masking agents such as peppermint oil or chlorophyll; immune reagents such as immunoglobulins or soluble antigens; local anesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino
35 acids, essential fats, vitamins and minerals; antioxidants such as thymol, alpha-tocopherol and butylated hydroxy toluene; lipopolysaccharides; complexing agents such as polymyxin; quaternary ammonium compounds such as benzalkonium chloride

and cetyl pyridinium chloride; aromatics such as camphor, eucalyptus oil, and aldehyde derivatives such as benzaldehyde; denture adhesives such as lower alkyl vinyl ether-maleic acid or anhydride copolymers and their salts; coolants having therapeutic efficacy such as menthol; or peroxides such as urea peroxide. It is
5 recognized that in certain forms of therapy, combinations of these agents in the same delivery system may be useful in order to obtain an optimal effect. Thus, for example, an antimicrobial and an anti-inflammatory agent may be combined in a single delivery system to provide combined effectiveness. Preferred actives are nutritional, therapeutic, medicinal, pharmaceutical, and those commonly used in
10 health care products.

Preferred formulations for the present invention compositions which comprise one or more actives are dental care preparations such as dentifrices and oral rinses, and cough/cold preparations in liquid oral dosage forms. Actives commonly utilized in cough/cold preparations include but are not limited to decongestants such as
15 pseudoephedrine hydrochloride, phenylpropanolamine hydrochloride, and ephedrine hydrochloride; antitussives such as dextromethorphan, chlorphedianol, carbetapentane, noscapine, codeine, hydrocodone, hydromorphone; analgesics such as acetaminophen and ibuprofen; expectorants or mucolytics such as glyceryl guaiacolate, guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and
20 ambroxol; antihistamines such as chlorpheniramine maleate, azatadine, doxylamine succinate, brompheniramine maleate and diphenhydramine hydrochloride; and non-sedating antihistamines such as astemizole, acrivastine, ketotifen, and terfenadine. These components as well as others are described in the following: U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, and U.S. Patent 4,783,465 to
25 Sunshine et al., issued November 8, 1988 which are incorporated herein by reference. Also useful are bronchodilators such as theophylline and albuterol; and stimulants such as caffeine.

Oral forms of cough/cold preparations comprise a safe and effective amount of one or more active components. Solid oral dosage forms preferably contain from
30 about 5% to about 95%, more preferably from about 10% to about 95%, and most preferably from about 25% to about 95%, of the active components. Liquid oral dosage forms preferably contain from about 1% to about 50%, more preferably from about 1% to about 25%, and most preferably from about 3% to about 10%, of the active components.

35 Dental care preparations typically comprise a soluble fluoride ion source as one of the actives. The soluble fluoride ion source is used in an amount sufficient to provide from about 10 to about 5000 ppm of the fluoride ion. Preferred fluorides are

sodium fluoride, stannous fluoride, indium fluoride, and sodium monofluorophosphate. Norris et al., U.S. Patent 2,946,735, issued July 26, 1960 and Widder et al., U.S. Patent 3,678,154, issued July 18, 1972, disclose such salts as well as others. Both patents are incorporated herein by reference in their entirety.

5 Various polymers and mixtures thereof are also useful in dental care preparations. These polymers may be synthetic anionic polymeric polycarboxylates and their complexes and/or carboxyvinyl polymers. Polymers useful in the present compositions are disclosed in U.S. Patent 4,906,456 to Gaffer et al., issued March 6, 1990, incorporated herein by reference in its entirety.

10 Pyrophosphate salts are pharmaceutical actives that may also be included in dental care preparations. Any of the alkali metal pyrophosphate salts may be used in either their hydrated or unhydrated forms. Specific salts include tetra alkali metal pyrophosphate, dialkali metal diacid pyrophosphate, trialkali metal monoacid pyrophosphate and mixtures thereof, wherein the alkali metals are preferably sodium
15 or potassium. Pyrophosphate salts are described in more detail in Kirk & Othmer, Encyclopedia of Chemical Technology, Second Edition, Volume 15, Interscience Publishers (1968), incorporated herein by reference in its entirety. The amount of pyrophosphate salt useful is any effective amount and is generally enough to provide at least 1.0% $P_2O_7^{-4}$ preferably from about 1.5% to about 6%, and more preferably
20 from about 0.5% to about 6%, to the compositions. It is to be appreciated that the level of $P_2O_7^{-4}$ is that capable of being provided to the composition (i.e., the theoretical amount at an appropriate pH) and that other pyrophosphate forms (e.g., $HP_2O_7^{-3}$) may be present when a final product is established.

25 Anti-plaque and anti-gingivitis pharmaceutical actives may also be included in the dental preparations. These actives include quaternary ammonium compounds or bis-biguanides such as chlorhexidine and stannous ion in the form of a combination of stannous fluoride and stannous gluconate. Oral compositions comprising stannous ion are described fully in U.S. Patent 5,004,597 to Majeti et al., issued April 2, 1991, incorporated herein by reference in its entirety. Disinfectant agents like triclosan and
30 antiseptic agents like thymol may also be included in the dental preparations.

35 Pharmaceutical actives commonly utilized in gastrointestinal products are those agents which are safe and effective when administered orally for treating disorders of the upper gastrointestinal tract which result in symptoms of upper gastrointestinal tract distress. Compositions for relieving gastrointestinal distress may include antacid agents, acid secretion prevention agents, other pharmaceutical actives and mixtures thereof.

Antacid agents include aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium aluminosilicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, sucralfate, sodium bicarbonate, and mixtures thereof. Acid secretion prevention agents include cimetidine, ranitidine, famotidine, omeprazole, and mixtures thereof. Other useful pharmaceutical actives include antifatulent agents such as simethicone and bismuth-containing agents such as, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgallate, and mixtures thereof. The pharmaceutical actives comprise from about 1% to about 99%, and preferably from about 25% to about 60% by weight of the composition.

The one or more actives are used in the present compositions at levels of from about 0.001% to about 99%, and preferably from about 0.01% to about 90%, by weight of the compositions.

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the present invention. Percentages are by weight unless otherwise stated.

Example I

Toothpaste Composition

A toothpaste composition according to the present invention is prepared having the following components:

	<u>Component</u>	<u>Weight %</u>
	Eugenol Monophosphate	0.300
30	Purified Water	10.422
	Sorbitol	60.565
	Sodium Fluoride	0.243
	Saccharin	0.130
	Colorant	0.500
35	Silica	20.000
	Spearmint Flavor	0.500
	Carbopol	0.300

	Xanthan Gum	0.475
	Trisodium Phosphate	1.450
	Monosodium Phosphate	0.590
	Sodium Alkyl Sulfate Solution	4.000
5	(27.9% in H ₂ O)	
	Titanium Dioxide	0.525

Add sorbitol to water and mix. Dissolve salts, eugenol monophosphate, sodium fluoride, saccharin, tridosium phosphate, monosodium phosphate, and then add colorant. Adjust to pH 7.0-8.5. Separately combine silica, carbopol, and xanthan gum and then slowly add this mixture to the composition while mixing continuously. Add sodium alkyl sulfate. Add spearmint flavor. Mix for ten more minutes.

Example II

Oral Mouth Rinse Composition

15 An oral mouth rinse composition according to the present invention is prepared having the following components:

	<u>Component</u>	<u>Weight %</u>
	Thymol Monophosphate	0.300
	Ethanol (190 proof)	16.250
20	Polysorbate 80	0.120
	Glycerin	10.000
	Purified Water	73.1218
	Benzoic Acid	0.0045
	Cetylpyridinium Chloride	0.045
25	Domiphen Bromide	0.005
	Sodium Saccharin	0.060
	Colorant	0.040
	Sodium Benzoate	0.0537

30 To ethanol, add all ingredients except thymol monophosphate and mix for 5 minutes. Add thymol monophosphate last and then adjust the pH of the composition to pH 6.5-8.5.

Example III

Liquid Oral Dosage Form

35 A liquid oral dosage form composition according to the present invention is prepared having the following components:

<u>Component</u>	<u>Weight %</u>
------------------	-----------------

	Menthyl Triphosphate	0.300
	Sucrose (x fine granular)	51.000
	Polysorbate 80	0.020
	Glycerin	2.000
5	Propylene Glycol	15.000
	Sodium Citrate, dihydrate	0.522
	Citric Acid	0.338
	Potassium Sorbate	0.100
	Dextromethorphan Hydrobromide	0.133
10	Guaifenesin	1.333
	Flavor	0.300
	Distilled Water	18.954
	Alcohol	10.000

- Mix together sucrose and about 1/3 the amount of water and heat to about 60°C until sucrose is dissolved. Mix in polysorbate 80 and glycerin. Separately mix together propylene glycol, sodium citrate dihydrate, menthyl monophosphate, citric acid and about 1/3 the amount of water. Separately mix together potassium sorbate and about 1/3 the amount of water. Add flavor. Mix together sucrose solution with propylene glycol solution. Mix together this solution and potassium sorbate solution. Lastly, add flavor solution. Adjust water level for proper batch size. Adjust pH to about 6.5-8.5. Mix for 30-35 minutes.

Example IV

Chewable Tablet

- A chewable tablet composition according to the present invention is prepared having the following components:

	<u>Component</u>	<u>Weight %</u>
	Calcium Carbonate and mannitol (50:50 wgt ratio)	88.0
	Powdered Mannitol	5.085
30	Aspartame	0.178
	Sodium Saccharin	0.092
	3-l-menthoxypropane-1,2-diol	0.300
	N-ethyl-p-menthane-3-carboxamide	0.025
	Menthyl monophosphate (a)	0.300
35	Peppermint Flavor	0.400
	Vanilla flavor	0.300
	Cola flavor	0.070

Blue speckles	0.750
Talc	2.000
Magnesium Stearate	2.500

(a) prepared as described below

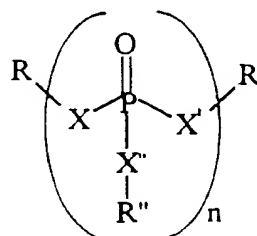
- 5 Mill N-ethyl-p-menthane-3-carboxamide to assure that it is in powder form. Dry mix all ingredients, except magnesium stearate, until uniformly mixed. Add magnesium stearate and mix for 1-2 minutes. Press desired amount into tablet (target is 550 mg/tablet).

Preparation of Menthyl Monophosphate

- 10 In a two-liter, three-neck round bottom flask cooled in an ice/water bath and equipped with a mechanical stirrer and an addition funnel, 153 mL of triethylamine is added to 157 g. of l-menthol in 186 mL of phosphorus oxychloride. After allowing the stirred suspension to warm to room temperature over 1 hour, the mixture is recooled to 0C, 500 mL of ether is added, and the mixture is carefully hydrolyzed
- 15 with 500 mL of water. After 1.5 hours at 0C, the mixture is allowed to warm to room temperature overnight. The aqueous layer is then extracted with diethyl ether (3 x 500 mL) and the combined ether layers are extracted with a 1 N sodium hydroxide solution (4 x 1 L.). After back-extracting the combined basic extracts with more ether (2 x 500 mL), the basic solution is acidified with concentrated
- 20 hydrochloric acid solution to pH 0. A yellow, oily product is removed and the remaining aqueous layer is extracted with three, one-liter portions of ether. The oil is dissolved in the combined ether extracts, the ether solution is dried with sodium sulfate, the mixture is filtered, and the solution is concentrated under vacuum to give a viscous syrup. After drying the product further in a vacuum oven, a white powder
- 25 is obtained which can be purified by crystallization from an acetone/water mixture.

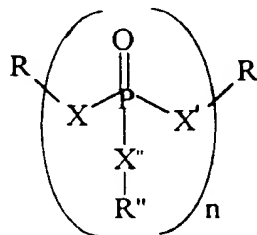
WHAT IS CLAIMED IS:

1. A composition comprising:
 - (a) from 0.001% to 25% of one or more phosphate derivatives having the structure:



wherein R is selected from the group consisting of a coolant component, a sweetener component, and a flavorant component;
 wherein R' and R'' are independently selected from the group consisting of R, an adherent component, M⁺, M⁺⁺, C⁺, and hydrogen;
 wherein X, X', and X'' are independently selected from the group consisting of oxygen, nitrogen and sulfur;
 n is an integer from 1 to 3; and
 (b) from 75% to 99.999% of carrier materials;
 and wherein further the composition is in a form suitable for oral or topical administration.

2. The composition according to Claim 1 wherein R'=R'', preferably wherein R' and R'' are independently selected from the group consisting of calcium, zinc, magnesium, manganese, copper and stannous.
3. A composition comprising:
 - (a) from 85% to 99.99% of one or more phosphate derivatives having the structure:



wherein R is selected from the group consisting of menthol, 3-l-menthoxypropane-1,2-diol, menthone glycerol acetal, menthyl lactate, methyl salicylate, saccharin, mannitol, sorbitol, glucose, sucrose, fructose, neohesperidin dihydrochalcone, eugenol, vanillin, thymol, cinnamaldehyde glycerol acetal, and linalool;

wherein R' and R'' are independently selected from the group consisting of R, C12-C18 diacyl glycerol, partially hydrolyzed vinyl acetate/ethylene copolymer, cellulose, chitin, glucosamine, silica gel, glycerol, lower alkyl vinyl ether-maleic acids, M⁺, M⁺⁺, C⁺, and hydrogen;

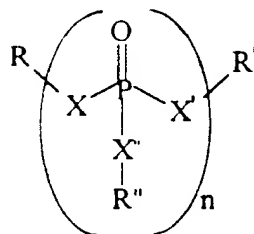
wherein X, X', and X'' are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

wherein n is an integer from 1 to 3; and

(b) from 1% to 99% of carrier materials;

and wherein further the composition is in a form suitable for oral or topical administration.

4. The composition according to Claim 3 wherein M⁺ is sodium or potassium, M⁺⁺ is selected from the group consisting of calcium, zinc, magnesium, manganese, copper, and stannous, and C⁺ is selected from the group consisting of ammonium, protonated amines, and partially or fully protonated amine-containing polymers.
5. The composition according to Claims 3 or 4 wherein R'=R'', preferably wherein R' and R'' are selected from the group consisting of calcium, zinc, and magnesium, manganese, copper and stannous.
6. A composition suitable for oral administration comprising:
 - (a) from 85% to 99.99% of one or more phosphate derivatives having the structure:



wherein R is a coolant component selected from the group consisting of menthol, 3-l-menthoxypropane-1,2-diol, menthone glycerol acetal, menthyl lactate;

wherein R' and R'' are hydrogen;

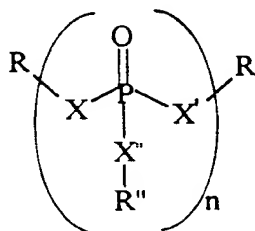
wherein X, X' and X'' are oxygen;

wherein n is an integer from 1 to 3; and

(b) from 1% to 99% of carrier materials;

and wherein further the composition is in a form suitable for oral or topical administration.

7. The composition according to Claim 6 wherein R is menthol and n is 1.
8. A composition comprising:
 - (a) from 85% to 99.99% of one or more phosphate derivatives having the structure:



wherein R is selected from the group consisting of methyl salicylate, eugenol, vanillin, thymol, cinnamaldehyde glycerol acetal, and linalool;

wherein R' and R'' are hydrogen;

wherein X, X', and X'' are O;

wherein n is an integer from 1 to 3; and

(b) from 1% to 99% carrier materials;

and wherein further the composition is in a form suitable for oral or topical administration.

9. The composition according to Claims 1-8 further comprising a safe and effective amount of one or more actives.
10. The composition according to Claim 9 wherein R is thymol and n is 1.
11. The composition according to Claim 9 wherein R is eugenol and n is 1.

12. The composition according to Claims 1-11 wherein the composition is in the form of an oral mouth rinse.
13. The composition according to Claims 1-11 wherein the composition is in the form of a dentifrice.
14. The composition according to Claims 1-11 wherein the composition is in a liquid oral dosage form.
15. The composition according to Claims 1-11 wherein the composition is in the form of a chewable tablet.
16. The composition according to Claim 1-11 wherein the composition is in the form of a nasal spray.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/10044

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K7/16 A61K7/48 A61K7/06 A61K7/00 A23L1/226
A23G3/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K A23L A23G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 7136, Derwent Publications Ltd., London, GB; AN 71-58875S & JP,A,46 031 559 (MIYAZOE) 1900 see abstract ---	1,3,6,9, 12-15
X	LU,A,68 497 (WILKINSON SWORD LIMITED) 7 December 1973 see the whole document ---	1,9, 12-16
X	EP,A,0 387 024 (PROCTER & GAMBLE) 12 September 1990 see the whole document ---	1,9, 12-15
X	EP,A,0 512 599 (UNILEVER) 11 November 1992 see the whole document ---	1,3,9, 12-15
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

11 January 1995

Date of mailing of the international search report

27.01.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Fischer, J.P.

International Application No
PCT/US 94/10044

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/10044

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
LU-A-68497	07-12-73	GB-A- 1434728 AU-A- 5988973 BE-A- 805123 CA-A- 1020336 CH-A- 583002 DE-A- 2345156 FR-A, B 2200011 JP-C- 1147507 JP-A- 49132016 JP-B- 57035218 NL-A- 7312935 SE-B- 409815 US-A- 4070496	05-05-76 06-03-75 16-01-74 08-11-77 31-12-76 28-03-74 19-04-74 26-05-83 18-12-74 28-07-82 29-03-74 10-09-79 24-01-78
EP-A-0387024	12-09-90	US-A- 4990328 AU-A- 5110690 CA-A- 2010572 JP-A- 3200718 US-A- 5068100	05-02-91 13-09-90 09-09-90 02-09-91 26-11-91
EP-A-0512599	11-11-92	US-A- 5202111	13-04-93
BE-A-678243	01-09-66	AU-B- 411533 AU-A- 5675565 CH-A- 535048 DE-A- 1617369 FR-M- 213 GB-A- 1115370 NL-A- 6603802 SE-B- 357493 US-A- 3471613	08-03-71 07-09-67 31-03-73 15-07-71 26-09-66 02-07-73 07-10-69
US-A-5244651	14-09-93	JP-A- 5070358 JP-A- 5117157	23-03-93 14-05-93
DE-A-2330384	09-01-75	NONE	